

REMARKS

Claims 10, 13-15, 39-50, and 72-84 are pending in the application. Claims 1-9, 11-12, 16-38, and 51-72 are canceled. Claim 10 is amended to correct informalities objected to by the Examiner. Claims 10, 43, 72, and 74 are amended herein to recite the phrase, "in a pharmaceutically acceptable carrier." Claim 76 is amended to properly depend from claims 10, 43, 72, and 74. Support for these amendments can be found at least at page 14, lines 20-38, and page 15, lines 1-10. Accordingly, no new material has been added.

Claim Objections

Claim 10 is objected to because the recited oligonucleotide is not properly labeled in accordance with the Sequence Rules. Applicants have amended Claim 10 to correct the informality. As such, this objection is moot.

Rejections under 35 U.S.C. §112, First Paragraph, Enablement

The rejection of claims 10, 13-15, 39-50, and 72-76 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement, was maintained.

The claims are drawn to a method of inhibiting tumor growth in a mammal by administering to the mammal a nucleic acid comprising an antisense sequence which is complementary to the 5' portion of the AAH sequence comprising cggaccgtgca (nucleotides 1-11 of SEQ ID NO:3) in a pharmaceutically acceptable carrier.

On page 2 of the Office Action, the Examiner states:

The instant claims are directed to the anti-sense modulation of the human AAH, and read on the inhibition of tumor growth in a human patient by the administration of a nucleic acid vector which transcribes a polynucleotide which is complementary of the HAAH regulatory coding sequence which is not disclosed.

Contrary to the Examiner's comment, disclosure of a polynucleotide that is complementary to the 5' portion of SEQ ID NO:3 recited in the claims is provided in Example 5 of the originally-filed specification:

To make an HAAH antisense construct, the full length human HAAH cDNA was inserted in the opposite orientation into a retroviral vector containing a G418 resistant gene, and antisense RNA was produced in the cells.

One of skill in the art reading the paragraph from the specification quoted above regarding “HAAH cDNA was inserted in the opposite orientation into a retroviral vector containing a G418 resistant gene, and antisense RNA was produced in the cells” would understand that the polynucleotide of the claims is described.

The Examiner goes on to say:

In the event that the claims were drawn to encompass a complementary coding region within SEQ ID NO:3, the specification is not enabling for the claims requiring the inhibition of tumor growth in a mammal, which reads on the treatment of a human patient with a naturally occurring tumor for the following reasons.

The reasons articulated by the Examiner pertain to the general field of antisense therapy and not to the invention itself - i.e., the use of AAH antisense sequences to inhibit tumor growth. The Examiner cited Li and Huang (Molecular Pharmaceuticals, 2006, Vol. 3, pp. 2805-2809) and Sundaram et al. (Nucleic Acids Research, 2007, Vol. 35, pp. 4396-4408) to support the position of the alleged unreliability in the art with respect to *in vivo* antisense treatment. This ground of rejection is again respectfully traversed.

First, Example 5 of the specification and Figure 9 provides evidence of the effectiveness of antisense oligonucleotides of the present invention in changing morphology and decreasing growth of FOCUS cells *in vitro*.

Furthermore, Applicants hereby submit data showing that antisense constructs encompassed by the claims inhibit tumor growth and progression in an art-recognized animal tumor model. Enclosed is a declaration from Jack R. Wands and Suzanne de la Monte describing studies using 9L gliosarcoma cells that were transfected *in vitro* with AAH antisense oligonucleotides and transplanted into rat brains. Brain sections were taken at various time points post-transplantation and prepared for histological examination. Data showed that 7 days post-transplantation, tumor mass was substantially smaller (decreased 50-75% in tumors containing AAH-oligo transfected tumor cells) than in control brains. In addition, the data show that brains transplanted with cells treated with AAH antisense oligonucleotides were characterized by tumors with decreased cell density compared to the tumors of control brains. Moreover, the presence of finger-like projections, an indicator of proliferative invasiveness of this tumor type, was reduced or entirely absent in antisense treated tumors. The description and data in the originally-filed specification and subsequent animal data provide ample guidance to instruct the skilled artisan to make and use the claimed invention. Applicants have more than

adequately overcome this rejection by providing evidence of the effectiveness of the oligonucleotides of the present claims in the treatment of malignant neoplastic tissues.

The rejection further states that the specification does not provide adequate disclosure of the "...what comprises a therapeutically effective amount of the complementary sequences of the claims.

Applicants respectfully disagree.

The specification states at page 15, lines 8-10, that while dosages must account for individual variation of the subject's physical characteristics, a general dosage for intravenous administration of nucleic acids is " 10^6 to 10^{22} copies of the nucleic acid molecule." The specification further states, at page 14,

"A therapeutically effective amount of a compound is an amount which is capable of producing a medically desirable result such as reduced production of an HAAH gene product or a reduction in tumor growth in a treated animal."

The originally-filed specification provides to the practitioner enough information to allow the dosage and delivery of the nucleic acids in a therapeutically effective manner, and thus to practice the claimed invention, without requiring undue experimentation. The present invention was not intended to provide, nor does it claim, a particularly new way or new dosage amount for antisense therapy. The specification provides ample guidance on how, and in what amounts, to administer the antisense molecules, in a manner which allows the clinician to use her/his judgment under the particular circumstances of the patient. Such judgments are not deemed to require undue experimentation under the patent law.

Finally, the Examiner states at page 3 of the Office Action that the particular art of antisense therapy in patients is not mature. The Examiner asserts that major technical hurdles pertaining to stability of the administered nucleic acid *in vivo* and uptake of an adequate amount of the administered nucleic acid still remain as problems seven years after the priority date of the instant application. Although in some cases, details pertaining to stability and uptake of nucleic acids may need to be resolved, Applicants submit that those details do not rise to the level of undue experimentation or unpredictability once the target sequence (in this case, AAH) has been identified. The art at and before the time of filing of this application together with the disclosure of the originally-filed specification was sufficient to fulfill the requirements of § 112.

APPLICANTS: Wands et al.
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For instance, in 1998, Isis Pharmaceuticals received approval from the Food and Drug Administration (FDA) to market and distribute Vitravene® (fomivirsen sodium), an antisense oligonucleotide, which is administered as naked DNA, to treat cytomegalovirus retinitis in AIDS patients (see Patil et al. DNA-Based Therapeutics and DNA Delivery Systems: A Comprehensive Review. The AAPS Journal 2005; 7(1) Article 9, pp.E61-E77; courtesy copy enclosed).

The Examiner is reminded that she has the burden of proving that Applicants have not taught how to make and use the claimed invention. Applicants respectfully contend that this burden has not been met. While the Examiner cites publications that describe struggling with certain antisense technologies, Applicants have cited ample evidence that the state of the art at the date of filing was not new and that, in fact, the FDA had already approved one or more antisense therapies for the market.


For all of the foregoing reasons, Applicants submit that the rejection of the pending claims should be withdrawn.

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CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If the Examiner believes any issues remain that could be resolved by a telephone conference, she is invited to contact the undersigned at the number listed below.

Respectfully submitted,



Ingrid A. Beattie, Reg. No. 42,306
Attorney for Applicant
c/o MINTZ LEVIN
One Financial Center
Boston, Massachusetts 02111
Tel.: (617) 542 6000
Fax: (617) 542-2241

Date: July 15, 2008

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